REMARKS

Claims 7, 39-44 are pending in this application.

The Amendments

The amendments in Claims 7, 40, 43 and 44 are supported, for example, by Figure 1; page 5, lines 16-20; page 7, line 14, to page 8, line 6; page 8, lines 29-34; page 11, lines 28-34; and page 37, line 32 to page 38 line 18.

No new matter is added in the amendments. The Examiner is respectfully requested to enter the amendments.

The Response

Objections to Claim 7

The Examiner maintains the objection of Claim 7 for the following reasons:

Part of Claim 7 is directed to the non-elected invention.

Applicants have amended Claim 7 by adding the term "mRNA" before the term "expression level". As a result, Claim 7 is directed to a method of detecting prostate or breast cancer, comprising determining the *mRNA expression level of a gene* encoding PAA3 protein, but not determining the PAA3 protein level expression. Thus, the amendment renders the objection moot.

Claim 7 uses the term "first individual" without reciting any subsequent individual.

Applicants have deleted the term "first" and thereby render this objection moot.

Claim 7 uses the language "higher".

Applicants have changed the term "higher" to "an increased" as suggested by the Examiner.

In view of above amendments and arguments, the objections to Claim 7 should be withdrawn.

35 U.S.C. §112 First Paragraph Rejection, Non-Enablement

The Examiner maintains the rejections of Claims 7 and 39-43 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in

such a way as to enable one skilled in the art to which it pertains to make and/or use the invention.

The Examiner asserts that there is no disclosure in the specification of the quantification of starting mRNA or cRNA. Thus, the Examiner is concerned that the genes expressed as cRNAs bound to the oligonucleotide arrays are not representative of the original mRNA such that the over-expression of PAA3 gene may be an experimental artifact.

Applicants respectfully disagree with the Examiner and would like to point out that the quantification of both mRNA and cRNA is clearly described in the specification. Page 63 lines 1-5 describes in detail how to isolate the original mRNA (poly A+ RNA) from the original total RNA. Page 63 line 12 of the specification also states that 1 μg of the poly A+ (mRNA) should be used for the array assay. Subsequently, the experiments in the present invention are carried out not only with an equal amount of the starting total RNA but also with an equal amount of the starting mRNA. As a result, the cRNAs bound to the arrays are representative of the original mRNA.

The Examiner is also concerned that the present invention did not identify the abundance of SEQ ID NO: 1 as was done by Lockhart *et al.*, and that as a result, it is allegedly not clear how abundant the mRNAs of SEQ ID NO: 1 are in prostate cells and the mRNAs may not be represented in cRNAs.

Applicants respectfully disagree with the Examiner. First, Lockhart *et al* do not teach or suggest that identification of frequency and abundance of a gene is necessary for the detection of *differential expression* of genes. Lockhart *et al.* are only concerned with the absolute quantitation of mRNA level in a range of concentrations for a number of cytokines. In contrast, the present invention is directed to methods of detecting the *differential expression* of cancer genes. The absolute quantitition of the mRNA is not important to the present invention. Secondly, Lockhart *et al.* were published in 1996, which is almost 8 years ago. Microarray techniques have grown tremendously in the past decade. As indicated in the Affymetric website, GeneChip® probe arrays provide a particular powerful tool to drug discovery because of their "unsurpassed sensitivity, specificity, and reproducibility" [give specific web site address]. Their ability to assess the contribution of nonspecific signals in a probe-specific manner allows the detection and quantitation of *low abundance transcripts*.

As a matter of fact, the present methods displayed high sensitivity and reproductivity in identifying such differential expressions. For instance, the present methods detect the difference in expression levels of PAA3 genes in prostate and breast cancer cells but not in other cancer cells in comparison to normal cells derived from various tissues. The experiments were repeated in at least 54 different primary prostate tumors and at least 90 control samples made up of body tissues, including adrenal gland, aorta, aortic valve, bladder, bone marrow, brain, breast, colonic epithelium, etc. The PAA3 gene expression is found to be more than 10 folds higher in prostate cancer cells than in normal prostate cells (page 70, lines 16-19). Such a substantial difference can hardly be an experimental artifact.

Therefore, the assays described in the specification are reliable, and are supported by those of ordinary skill in the art.

35 U.S.C. §112 First Paragraph Rejection – Lack of Written Description

Claims 7 and 40-43 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not containing a written description of the invention in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

The Examiner asserts that gene encompasses genomic structures and the specification fails to describe the 5' and 3' regulatory regions and the structure of which are not conventional in the art.

Applicants have amended Claim 7 by changing the term "gene" to "DNA", thereby rending the rejection moot.

The Examiner also asserts that a probe that is complementary to SEQ ID NO: 1 encompasses unrelated sequences with unknown structure.

Applicants have amended Claim 7 to recite that the nucleic acid probe is completely complementary to SEQ ID NO: 1. Given that the sequence of SEQ ID NO: 1 is disclosed in the present application, the sequence of a probe that is completely complementary to SEQ ID NO: 1 is identifiable by using the basic A-T/G-C matching rules in the art of molecular biology. The specification also indicates the characteristics of the probes, such as strandedness and length (page 18, line 29 to page 19 line 17). Accordingly, a probe that is completely complementary to SEQ ID NO: 1 is not unrelated sequences with unknown structures because its sequence and

characteristics are readily identifiable to those skilled in the art in view of the disclosure of the present application.

Therefore, the § 112 first paragraph rejection of Claims 7 and 40-43 should be withdrawn.

35 U.S.C. §112 First Paragraph Rejection, Scope

Claims 40-42 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly for lack of enablement for a probe "complementary" to SEQ ID NO: 1.

Claim 40 is amended to recite that the expression is measured using a nucleic acid probe completely complementary to SEQ ID NO: 1. The specification discloses the characteristics and generation of a probe "completely complementary" to SEQ ID NO: 1 (page 18, line 29 to page 19 line 17). Therefore, the specification provides enabling disclosure for a probe "complementary" to SEQ ID NO: 1. The §112 first paragraph rejection of Claims 40-42 should be withdrawn.

35 USC §102(e) Rejection

Claims 7 and 39-43 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Schlegel, *et al.* (PCT US 01/05171).

Claim 7 has been amended by adding "wherein said mRNA expression is measured using a nucleic acid probe completely complementary to SEQ ID NO:1." Because Schlegel, *et al.* do not disclose a nucleic acid sequence that is completely complementary to SEQ ID NO:1, Claim 7 is novel in view of Schlegel, *et al.* The §102(e) rejection of Claims 7 and 39-43 should be withdrawn.

CONCLUSION

Applicants believe that the application is in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 463-8109.

Respectfully submitted,

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